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A CASE OF MASSIVE ADRENAL MALIGNANT PHEOCHROMOCYTOMA: MANAGEMENT OF A LARGE PHEOCHROMOCYTOMA

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A 69-year-old man was referred to our hospital for a left abdominal tumor measuring about 30 cm in diameter. Laboratory examination revealed an elevation of norepinephrine in plasma and of its metabolites in urine. CT scan disclosed a huge cystic tumor in the retroperitoneal space and an enlarged aortocaval lymph node, suggesting a diagnosis of malignant pheochromocytoma. The hemodynamic studies showed low blood volume and high vascular resistance, and therefore, he was treated with vasodilators and volume expansion. His hemodynamic status normalized and a complete excision was performed. Pathological examination revealed that the patient had a pheochromocytoma with metastasis to a lymph node. The total weight of the tumor was 5,930 g. Since pheochromocytomas can become a large with a risk of malignancy, they should be surgically excised as completely as possible with further treatment after making a definite diagnosis.

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Key words: Pheochromocytoma, Malignant, Adrenal gland neoplasms, Preoperative care, Surgery

INTRODUCTION

Pheochromocytoma is a rare disease with an incidence of less than 1 per 100,000 person-years¹⁾. This chromaffin-cell-derived tumor has the ability to produce, store and secrete catecholamines²⁾. Thus, surgical intervention requires close attention to preoperative, intraoperative and postoperative management of the tumor³⁾. These considerations are no less important for large tumors.

We describe a case of massive adrenal malignant pheochromocytoma, in which we explain the preoperative management of the hemodynamic complications. Additionally, the management of a large pheochromocytoma is discussed.

CASE REPORT

A 69-year-old man was admitted to a local hospital because of a large palpable mass in the left upper quadrant in June 1983. He was diagnosed as having a pheochromocytoma because of hypertension, an increase in serum catecholamine levels and

a left retroperitoneal tumor on CT scan. Surgical exploration was done and a mass about 10 cm in size was found, but considered unresectable because it was tightly adhered to the surrounding tissue. However, the tumor gradually became larger after the operation until it finally reached a size of about 30 cm in diameter. He was then referred to Tokyo Women's Medical College Hospital in September 1992.

On admission, his blood pressure and heart rate were 165/95 mmHg and 88/min, respectively, while on prazosin. On physical examination a hard mass about 30 cm in diameter was protruding out from the left upper quadrant of the abdomen (Fig. 1). Complete blood count, serum electrolytes, BUN, creatinine, liver function test and urinalysis were all normal except for white blood cell of 3,500/mm³ and platelet of 10.2×10^4 /mm³. Creatinine clearance was slightly decreased at 33.7 ml/min. A glucose tolerance test showed moderate impairment. Plasma levels of epinephrine and norepinephrine were 0.03 ng/ml (normal ~0.10) and 0.62 ng/ml (normal 0.05~

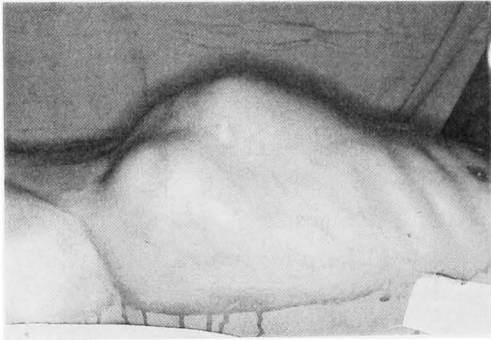


Fig. 1. Appearance of the patient. A huge tumor protruded out from the left upper quadrant of the abdomen.

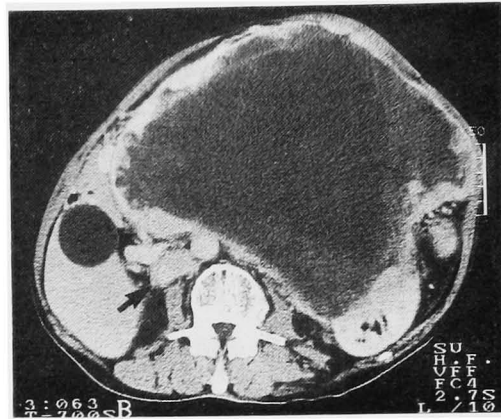


Fig. 2. CTscan of the abdomen. The huge cystic tumor displaced other organs and an aortocaval lymph node was enlarged

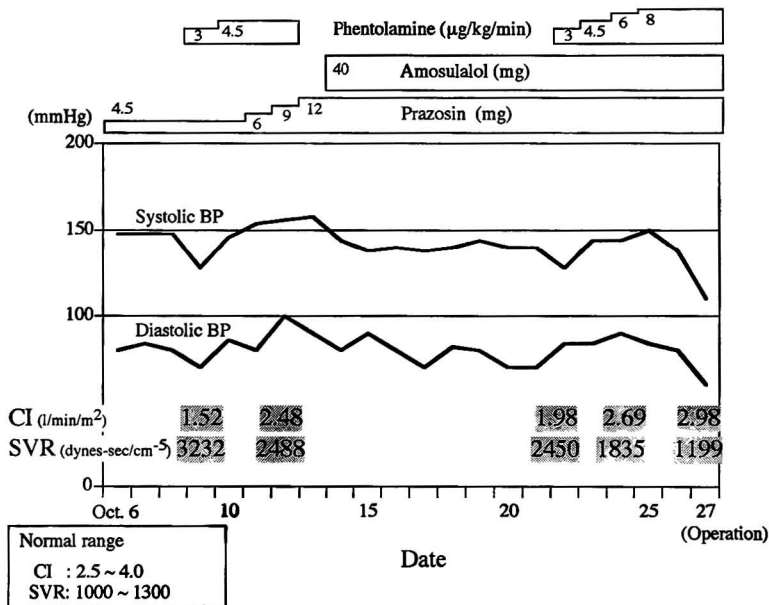


Fig. 3. Transition of preoperative parameter of hemodynamics. The use of α - and β -blocking agents led to normalization of hemodynamics parameters.

0.4), respectively. The 24-hour urinary excretion of catecholamines revealed a dopamine level of 2,100 μg (normal 100~1,000), a norepinephrine level of 541 $\mu\text{g/day}$ (normal 29~120), a vanillylmandelic acid (VMA) level of 213 mg/day (normal 1.5~7.5), and a homovanillic acid (HVA) level of 14.4 mg/day (normal 1~7).

CT scan revealed the tumor to be 27 \times 20 cm in size with multilocular cysts, displacement of other organs, and an en-

larged aortocaval lymph node (Fig. 2). The periphery of the tumor showed high intensity on the T2-weighted magnetic resonance image (MRI). Abdominal aortography demonstrated the displacement of main branches by the tumor and feeding arteries diverging from the splenic artery. On venous sampling from the inferior vena cava, the plasma level of norepinephrine above the right adrenal vein was 40% higher than the sample taken below the adrenal vein.

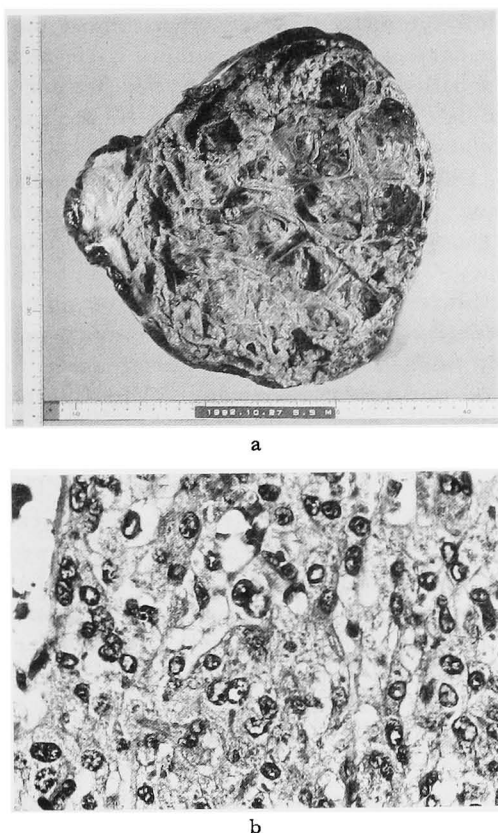


Fig. 4. Excised specimen. a: The cut-surface of the tumor. The interior turned into the multilocular fuse necrosis. b: Microscopic finding of the solid portion of the tumor. Large nuclei, mild pleomorphism and a few mitotic figures were seen.

These findings led us to conclude that the diagnosis was a pheochromocytoma. Using a Swan-Ganz catheter to evaluate the patient's hemodynamic status, we found that the cardiac index (CI) was decreased, and that the systemic vascular resistance (SVR) was elevated in spite of the long term use of prazosin (Fig. 3). The central venous pressure (CVP) was low at 0 cmH₂O. Because these parameters did not normalize after fluid therapy and the administration of α -blocking agents (prazosin and phentolamine), we added an α - and β -blocking agent (amosulalol) and, as a result, the CI and SVR normalized. CVP increased to 4 cmH₂O after fluid therapy.

Resection of the tumor and lymphade-

nectomy was performed with a subcostal transabdominal incision with midline extension. At laparotomy the tumor was adherent to the surrounding tissues specifically the pancreas, duodenum, upper jejunum and posterior wall of the abdomen. Collateral vessels were found on the surface of the tumor. Before manipulation, we aspirated the cystic fluid for the following two reasons: the first was to prevent compression of the vena cava by the tumor and the second was to make manipulation of the tumor easier.

The tumor weighed 5,930 g, was well encapsulated, and its interior showed multilocular fuse necrosis immersed by red brown serous fluid (Fig. 4a). On histological examination the solid portion of the tumor consisted of cells with abundant basophilic granules in the cytoplasm (Fig. 4b). The tumor cells formed a cordal network which was separated by a capillary rich stroma. Nuclei were large with mild pleomorphism and a few mitotic figures were present. We feel that the tumor was derived from the adrenal gland because no normal adrenal tissue was found in the specimen or grossly at laparotomy, suggesting complete replacement of the adrenal by tumor. An aortocaval lymph node 2 cm in diameter revealed nests of tumor cells. By flow cytometric nuclear DNA ploidy analysis, the tumor showed an aneuploid pattern. From these findings, the tumor was considered to be a malignant pheochromocytoma.

The early postoperative course was uneventful. CI and SVR had improved to 3.36 l/min/m² and 983 dynes-sec/cm⁻⁵, respectively, but intraabdominal bleeding suddenly occurred three weeks after operation. The patient was taken to the operating room and had an evacuation of large hematoma. This was felt to be due to hemorrhagic pancreatitis secondary to a pancreatic injury, as abdominal fluid was high in amylase. The patient was then admitted to ICU where he developed pneumonia and ARDS. The patient died on the 49th post-operative day from multi-organ failure.

DISCUSSION

Pheochromocytomas vary somewhat in size and may grow to be fairly large⁴⁾. In a study of 175 cases, most pheochromocytomas were found to weigh less than 100 g, but 4% exceeded 1,000 g⁵⁾. Pathologically, hemorrhage, necrosis and cyst formation often occurred in the larger tumor⁶⁾. Intratumor hemorrhage may cause cyst formation⁷⁾ and vasoconstriction in the tumor induced by excessive catecholamines may promote these changes⁸⁾.

Stein reported the correlation between tumor size and the duration of symptoms and calculated the mean doubling time to be nearly 24 months⁹⁾. Although the inside of the tumor became necrotic, this tumor had enlarged from 10 cm to 27 cm in diameter over 9 years as demonstrated by CT scan. This growth rate corresponded approximately to the mean doubling time described above and the tumor would have continued to expand unless we had treated the patient. Options for treatment of large pheochromocytoma include surgical excision, which we elected to use in this patient. Other options are similar to those for malignant pheochromocytoma which include combination chemotherapy with cyclophosphamide, vincristine, and dacarbazine¹⁰⁾, radiopharmaceutical ¹³¹I-M-IBG treatment¹¹⁾, and external beam tele-radiotherapy¹²⁾. However, their effectiveness in malignant pheochromocytoma has been reported to be lower than that of surgery¹⁰⁻¹²⁾. Therefore, successful surgical extirpations offer the best option for curative therapy¹³⁾, despite the higher risks of surgical interventions due not only to excessive catecholamine release but also from the size of the tumor itself.

We diagnosed our patient as having a malignant pheochromocytoma because of metastasis to a lymph node. Identification of malignancy was confirmed not by the histological studies, but by evidence of metastasis to the non-chromaffin tissue⁴⁾. Other indices in discriminating between malignant and benign tumor have been suggested. Hosaka proposed the usefulness of nuclear DNA ploidy analysis by

flow cytometry¹⁴⁾, while others stated that urinary excretion of dopamine is elevated in patients with malignant pheochromocytoma¹⁵⁾. Our findings supported the usefulness of those studies.

During the operation, tumor manipulation and resection can result in dramatic changes in blood pressure and arrhythmia¹⁵⁾. To reduce these risks, we routinely evaluate and correct the hemodynamic status of patients with pheochromocytoma by using a Swan-Ganz catheter prior to and during the operation. CVP, CI and SVR are good indices for the evaluation of abnormal hemodynamic states seen in patients with pheochromocytoma¹⁵⁾. The hemodynamic parameters of this patient before the preoperative treatment showed high SVR, low CVP and low cardiac output attributable to high catecholamines causing a decrease of intravascular volume. These were likely accountable for decreased creatinine clearance, as well.

Preoperative α -blockade can diminish preoperative clinical symptoms, reverse hypovolemia and stabilize blood pressure prior to and during surgery¹⁶⁾. However, the use of prazosin and phentolamine did not normalize the hemodynamic parameters in this case and required the additional use of an α - and β -blocking agent. Although Manger did not recommend the administration of labetalol, α - and β -blocker similar to amosulalol which may worsen hypertension¹⁶⁾, we feel that these drugs are effective in the preoperative management of some patients with pheochromocytomas.

This case demonstrates the complications of delayed treatment in a patient with pheochromocytoma. Although it is difficult to say what the outcome would have been 9 years ago if the patient had received therapy, one has to think that the risk of malignancy, as well as risk of surgery would increase with time. We believe that the best treatment for pheochromocytoma is prompt excision with proper management of any hemodynamic compromise associated with the disease.

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和文抄録

巨大副腎悪性褐色細胞腫の1例：大型の褐色細胞腫の管理について

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合谷 信行，中沢 速和，東間 紘

69歳男性。直径約 30 cm の左側腹部腫瘍の診断および治療のため当科へ紹介された。臨床検査により血中ノルエピネフリン値およびその尿中代謝産物の高値，CT スキャンにより巨大な嚢胞性後腹膜腫瘍，大動静脈リンパ節の腫大が認められ，悪性褐色細胞腫と診断された。血行動態学的に循環血液量の低下と血管抵抗値の上昇が認められたため，血管拡張剤の使用とともに循環血液量の補充が行われた。これらにより血

行動態は正常化し，腫瘍摘除術が施行された。病理学的に，リンパ節転移を伴う褐色細胞腫と診断され，腫瘍重量は 5,930 g であった。褐色細胞腫は比較的大きくなることがあり，これに伴い悪性化の危険も増加する可能性が高いと考えられる。したがって，可能なかぎり治癒切除を試み，確定診断および今後の治療方針を決定することが重要である。

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